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(12) APPLICATION FOR PATENT OF INVENTION A1

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(56) List of documents cited in the preliminary Search Report: Refer to the end of the present document

(60) References to other relevant national documents:

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(54) COMPOSITION FOR IMPROVING THE PHYSIOCHEMICAL
CHARACTERISTICS OF APATITE-BASED MATERIALS, ITS USE AND
PROCESS FOR ITS IMPLEMENTATION

(57) The invention concerns a composition comprising at least one titanium and fluorine derivative to reinforce natural or artificial apatite-based materials, notably teeth, bones, dental implants and surgical prostheses. The compositions of the invention notably permit an enrichment of titanium and fluorine in apatite-based materials, at a pH less than 6.

The invention also relates to a reinforcement process for apatite-based materials using the compositions of the invention.

The invention relates to a dental composition designed to improve the physiochemical characteristics of natural or artificial apatite-based materials, notably implants. It also relates to the use of titanium derivatives for reinforcement of apatite-based materials, as well as a process for reinforcement of apatite-based materials.

A large part of prostheses or implants for dental or medical usage is made from titanium.

The interest in titanium for the preparation of such prostheses or implants is well known. Its mechanical properties, its high corrosion resistance and its light weight have made it a material of choice for these applications.

In addition, titanium shows a very good compatibility with biological tissues. It generally does not alter the growth of osteoblasts, fibroblasts and gingival epithelial cells and is currently used in the manufacture of dental or bone prostheses to replace defective tissues, including intervertebral disks and the ossicles of the ear.

The very good compatibility between titanium and tissues based on apatite is explained by the formation, on the titanium surface, of a fine layer of titanium oxide able to protect the subjacent metal and to bond to the calcium atoms and to the phosphorus groups of the apatite.

Document WO 0105797 describes titanium derivatives as well as their use in compositions for oral use, as a protection agent against dental caries. This document describes the formation of a protective layer on the tooth surface by the titanium derivative, in the form of a glaze, under pH conditions varying from approximately 6.5 to approximately 7.5.

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The object of the invention is to propose a new composition for reinforcement of apatite-based materials, comprising derivative compounds of titanium and fluorine, capable of modifying the structure of the apatite.

A first subject of the invention thus concerns such a composition.

Another subject of the invention concerns the use of titanium and fluorine derivatives for the reinforcement of apatite-based materials.

Another subject of the invention concerns a process for the reinforcement of apatite-based materials.

Within the scope of the present invention, by the term "apatite-based materials" is meant natural hydroxyapatites, notably dental enamel, dentin, bones, as well as artificial ceramics based on calcium phosphate designed for medical applications, notably dental implants, devices for percutaneous or periodontal implantation, bone prostheses used notably in maxillo-facial or spinal orthopedic surgery.

The composition designed to reinforce apatite-based materials according to the invention is characterized in that it comprises at least one titanium and fluorine derivative conforming to the general formula (I) below

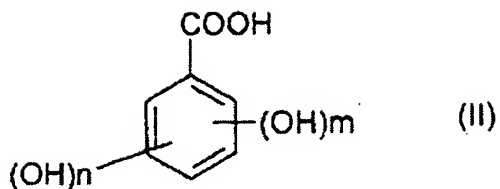


in which

x is a whole number varying from 1 to 6, and y is 0, 1 or 2, with the condition that when y is 0, x is not 4.

and R represents:

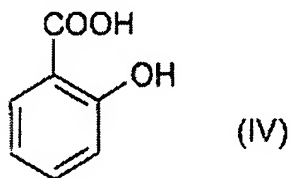
- a compound chosen from among K, Na or NH_4 , or
- a ligand L of formula (II) below:



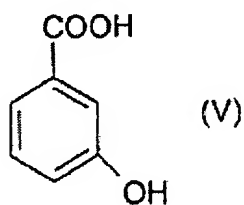
in which m is 0 or 1 and n is 0, 1 or 2;

the composition according to the invention is characterized in addition in that it has a pH less than or equal to 6 in the solubilized state, preferably in aqueous medium.

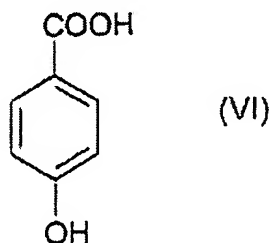
The ligands L that can be employed are notably benzoic acid derivatives, particularly 2-hydroxybenzoic acid of formula (IV) below and its derivatives:



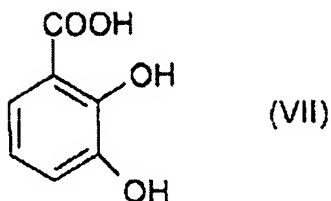
3-hydroxybenzoic acid of formula (V) below and its derivatives:



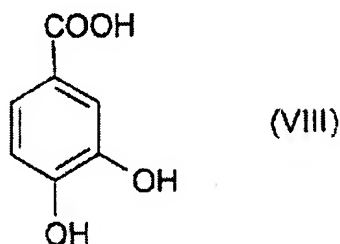
4-hydroxybenzoic acid of formula (VI) below and its derivatives:



2,3-dihydroxybenzoic acid of formula (VII) below and its derivatives:



3,4-dihydroxybenzoic acid of formula (VIII) below and its derivatives:



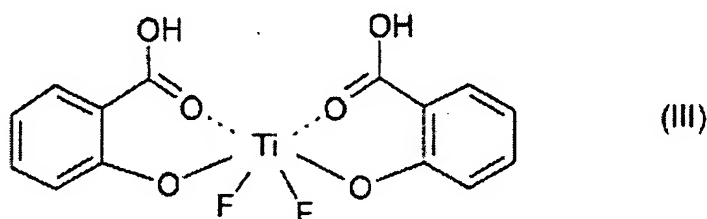
The compounds in which R represents a ligand of formula (II) can comprise one or more asymmetric carbon atoms. They can therefore exist in the form of enantiomers or diastereoisomers. These enantiomers and diastereoisomers, as well as their mixtures, including racemic mixtures, make up part of the invention.

The compounds in which R represents a ligand of formula (II) can exist in the state of bases or acid addition salts. Such addition salts make up part of the invention.

These salts are advantageously prepared with pharmaceutically acceptable acids, but salts of other useful acids, for example, for purification or isolation of compounds, also make up part of the invention.

The compounds in which R represents a ligand of formula (II) can also exist in the form of hydrates or solvates, i.e. in the form of associations or combinations with one or more water molecules or with a solvent. Such hydrates and solvates also make up part of the invention.

A first example of the titanium- and fluorine-derived compound according to the invention, obtained by using 2-hydroxybenzoic acid as ligand L, is the compound represented by formula (III) below:



Another example of the titanium and fluorine derivative according to the invention in which R represents a mineral compound is potassium hexafluorotitanate of the formula K_2TiF_6 .

Other examples of compounds usable within the scope of the invention are sodium hexafluorotitanate of formula Na_2TiF_6 and ammonium hexafluorotitanate of formula $(NH_4)_2TiF_6$.

Titanium and fluorine derivatives in which R represents a ligand L of formula (II) above can be prepared according to the method described in document WO 0105797.

The compositions of the invention have a titanium content varying from approximately 10 to approximately 1000 ppm, preferably approximately 300 ppm and a fluorine ion content varying from approximately 50 to approximately 1500 ppm, preferably approximately 240 ppm.

According to one form of execution, compositions according to the invention also comprise an additional fluorinated compound, notably a fluorine salt, for example sodium fluoride or sodium monofluorophosphate.

This additional fluorinated compound is present in the compositions of the invention in a quantity varying from approximately 50 to approximately 1500 ppm, preferably approximately 100 to approximately 500 ppm.

The compositions of the invention have a pH less than or equal to 6, preferably comprised between approximately 5 and approximately 1, in the solubilized state, depending on the mode of administration of the composition. The compositions of the invention are placed in solution preferably in aqueous medium, but can also be placed in solution, as a function notably of the titanium and fluorine derivative used, in an organic solvent such as ethanol.

It has been shown that at such pH values, the compositions of the invention permit the substitution of calcium atoms present in the apatite by titanium and the substitution of hydroxyl groups, bicarbonates or impurities present in the apatite by fluorine.

This substitution modifies the structure of the apatite and renders it more resistant, not only to acid erosion and dental caries, but also to abrasion, wear and traumatic shock.

The incorporation of an additional fluorinated compound increases still further the resistance of the apatite to dissolution by acids.

It goes without saying that the invention can be applied not only to dental enamel and dentin in compositions for oral use, but also to other natural apatites, for example bony tissues, or artificial apatites, such as ceramics.

The compositions of the invention can be present in the usual different forms for administration in a clinical situation (topical route) or for the preparation of artificial apatites.

In administration by topical route, the compositions of the invention can be present in the form, in the case of an oral application, of a dentifrice, a powder to be diluted, a spray, a chewing gum, a lozenge to suck, a dental gel, an oral implant such as a patch, a mouthwash, or a solution. For an application on bone or on an artificial apatite, the compositions of the invention can be present in the form of a solution, a gel, a paste, or a powder to be diluted.

All of these forms are themselves well known to the person skilled in the art. In addition to titanium-derived compounds, associated with a fluorine salt or not, the forms mentioned above can comprise excipients or conventional ingredients for each of these forms.

For example, the forms for oral application can contain anionic, amphoteric, zwitterionic, cationic or non-ionic surfactants. They can also comprise thickeners, binding agents, sweeteners, humectants or cooling agents, preservatives, coloring agents, whiteners, flavoring or masking agents, plant essential oils, plasticizers, peptizing agents, anti-tartar agents, inhibitors of the production of sulfurated volatile compounds such as zinc salts and complexes, cicatrizers, anti-bleeding agents, polishers, anti-dental plaque agents such as chlorhexidine, hexetidine, cetylpyridinium chloride, triclosan and/or enzymes such as dextranase, mutanase, lysozymes, lactoferrin or peroxidases.

Generally, the composition according to the invention administered by topical route comprises titanium-derived compounds in a quantity such that its titanium content is greater than 0.001% by weight, preferably comprised between 0.01 and 0.05% by weight with regard to the total weight of said preparation.

The composition according to the invention, when it is used to reinforce an artificial apatite-based structure, can comprise a greater quantity of titanium. For example, it can comprise titanium-derived compounds in a quantity such that its titanium content is greater than 0.001% by weight, preferably comprised between 0.01 and 0.1% by weight with regard to the total weight of said composition.

One example of the composition according to the invention, in the form of a powder to be diluted extemporaneously for administration by topical route comprises the following elements, expressed in percentages by weight with regard to the total weight of the composition:

- compound of formula III	9%
- mannitol	79%
- flavoring agent	8%
- sodium saccharinate	4%

From a tablet of 500 mg of the above compound, placed in solution in 20 ml of purified water, a solution containing 300 ppm of titanium is obtained, of pH comprised between 3.5 and 5.

Another example of the composition according to the invention, in the form of a powder to be diluted extemporaneously for the preparation of a solution for

reinforcement of artificial apatites, comprises the following elements, expressed in percentages by weight with regard to the total weight of the preparation:

- compound of formula III 100%

From a tablet of 750 mg of the above composition, placed in solution in 100 ml of purified water, a solution of pH approximately 3 and containing 1000 ppm of titanium is obtained.

When the composition of the invention is administered by topical route, the pH of the composition in the solubilized state is less than or equal to 6, preferably comprised between approximately 5 and approximately 2.

When the composition of the invention is used to reinforce an artificial apatite, the pH of the composition, once placed in solution, can be lower than in the case of use by topical route. In this case, the composition of the invention has a pH in solution less than or equal to 6, preferably comprised between approximately 4 and approximately 1.

The majority of titanium- and fluorine-derived compounds usable in the invention, for example the compound of formula (III), are acidic in aqueous solution. In certain cases, it is nevertheless necessary to adjust the pH of the composition so that it is less than or equal to 6. In other cases, it may also be necessary to increase the pH, when the composition is too acidic in the solubilized state.

The pH of the composition can be adjusted, as a function of the relative acidity of the titanium and fluorine derivatives used, by supplemental acid or alkaline agents, depending on the case. Such agents are known in and of themselves for this use in compositions designed to be administered to humans.

For example, usable acidic agents are notably citric acid, hydrochloric acid, lactic acid, phosphoric acid, and tartaric acid; and usable alkaline agents are notably sodium hydroxide, monoethanolamine, diethanolamine, and triethanolamine.

The subject of the invention is also the use of a composition comprising at least one titanium and fluorine derivative for the reinforcement of apatite-based materials.

According to the invention, the composition comprising at least one titanium and fluorine derivative is such as previously defined.

The invention is particularly useful for the reinforcement of natural or artificial apatite or hydroxyapatite such as previously defined.

The subject of the invention is also a process for the reinforcement of apatite-based materials.

The process of the invention is characterized in that it comprises the step consisting of applying a composition comprising a titanium and fluorine derivative such as previously defined onto the apatite-based material, said composition having, in the solubilized state, a pH less than or equal to 6.

According to the process of the invention, a step of treatment with an acidic or demineralized compound can be conducted before the application of the composition. Preferably, this treatment step is conducted by using an acidic or demineralizing agent such as citric acid, lactic acid, phosphoric acid, or tartaric acid.

According to one variant of execution of the process of the invention, the composition applied onto the apatite-based material to be reinforced comprises a titanium and fluorine derivative such as defined previously, and also comprises an

additional fluorinated compound, notably in the form of a salt, such as previously defined.

The examples that follow are for purposes of illustrating the invention.

In order to study the effects of the compositions of the invention on hydroxyapatite, compositions 1 and 2 according to the invention are prepared:

Composition 1: aqueous solution of potassium hexafluorotitanate (containing 200, 400 or 1000 ppm titanium) for a local application.

Composition 2: aqueous solution of the compound of formula III (containing 200, 300, 400 or 1000 ppm of titanium) for a local application.

Modification of the hydroxyapatite structure

The compositions above (of pH comprised between 1 and 6) are contacted with commercially obtained hydroxyapatite powder.

The hydroxyapatite composition after treatment was studied by x-ray photoelectronic spectroscopy.

The results obtained are indicated in Table I below.

Table I

	Ca	O	Ti	F	Ti/Ca	F/O
C	21,4	63,9				
X1	18,2	58,5	3,5	6,3	0,19	0,11
X2	18,3	57,1	3,8	7,5	0,21	0,13
Y1	14,2	61,0	6,2	5,5	0,44	0,09
Y2	13,0	60,3	7,3	6,0	0,56	0,10

C: control hydroxyapatite (treated with water)

[In the table commas represent decimal points—Trans. Note.]

X1 and X2: hydroxyapatite treated with composition 1 (solutions containing 200 and 400 ppm of titanium, respectively)

Y1 and Y2: hydroxyapatite treated with composition 2 (solutions containing 200 and 400 ppm of titanium, respectively).

These results show that the structure of hydroxyapatite is deprived of calcium and oxygen upon contact with the compositions of the invention and is enriched with titanium and fluorine, in proportion to the increased concentration of the solution applied.

The hydroxyapatite samples treated are analyzed by mass spectrometry. The percentage of calcium substituted by titanium and the percentage of hydroxyl groups substituted by fluorine are compared to those obtained after contact of the hydroxyapatite with a solution of sodium fluoride. The results obtained are indicated in Table II below.

Table II

Treatment of the hydroxyapatite	Substitution of Ca by Ti	Substitution of OH by F
NaF	0.3%	52.0%
X3	17.1%	63.0%
Y3	40.3%	55.3%

X3: composition 1 containing 1000 ppm of titanium

Y3: composition 2 containing 1000 ppm of titanium

NaF: sodium fluoride with a fluorine content of 1000 ppm.

These results show the simultaneous substitution of calcium by titanium and hydroxyl groups by fluorine with the tested solutions.

Modification of the composition of dental enamel after topical application

In order to evaluate the effects of treatment by local application, freshly-extracted human teeth are contacted with composition 2. An experimental window is defined on each tooth and separated into two parts. A moderate acid attack (dilute phosphoric acid for 1 minute) is conducted on the window. One half of the window is then isolated under wax, while the other half is exposed to treatment with composition 3 containing 300 ppm of titanium.

The enamel situated under the treated half is examined by scanning electron microscopy. Its titanium composition is determined by elemental analysis, by means of an x-ray photoelectronic spectroscope. The results show a modification of the hydroxyapatite that makes up the dental enamel, associated with the deep incorporation of titanium in the structure.

The results show that the invention permits not only the substitution of hydroxyl groups by fluorine, but also the substitution of calcium by titanium under conditions of local application of the composition of the invention, in acidic medium.

Claims

1. A composition designed to reinforce apatite-based materials, characterized in that it comprises at least one titanium and fluorine derivative conforming to the general formula (I) below:

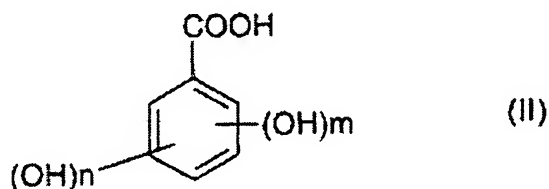


in which

x is a whole number varying from 1 to 6 and y is 0, 1 or 2, with the condition that when y is 0, x is not 4

and R represents:

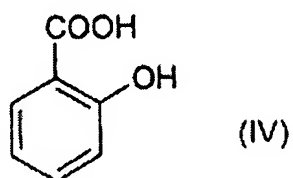
- a compound chosen from among K, Na or NH_4 , or
- a ligand L of formula (II) below:



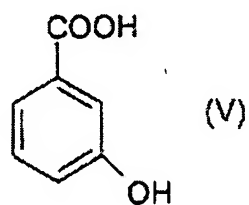
in which m is 0 or 1 and n is 0, 1 or 2;

the composition being characterized moreover in that it possesses a pH less than or equal to 6 in the solubilized state, preferably in aqueous medium.

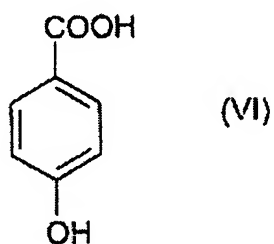
2. The composition according to claim 1, further characterized in that the ligands L are notably benzoic acid derivatives, notably 2-hydroxybenzoic acid of formula (IV) below and its derivatives:



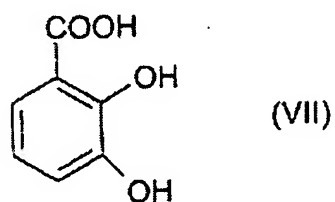
3-hydroxybenzoic acid of formula (V) below and its derivatives:



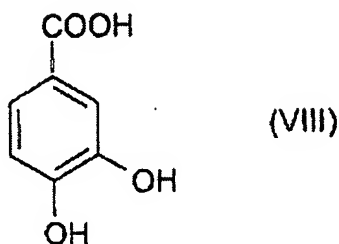
4-hydroxybenzoic acid of formula (VI) below and its derivatives:



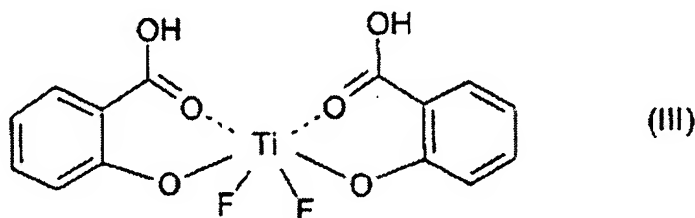
2,3-dihydroxybenzoic acid of formula (VII) below and its derivatives:



3,4-dihydroxybenzoic acid of formula (VIII) below and its derivatives:



3. The composition according to claim 1, further characterized in that the compound derived from titanium and fluorine is the compound shown by the following formula (III):



4. The composition according to claim 1, further characterized in that the titanium and fluorine derivative is notably potassium hexafluorotitanate of the formula K_2TiF_6 , sodium hexafluorotitanate of the formula Na_2TiF_6 , ammonium hexafluorotitanate of formula $(NH_4)_2TiF_6$.
5. The composition according to any one of claims 1 to 4, further characterized in that it has a titanium content varying from approximately 10 to approximately 1000 ppm, preferably approximately 300 ppm and a content of fluorine ions varying from approximately 50 to approximately 1500 ppm, preferably approximately 240 ppm.

6. The composition according to any one of claims 1 to 5, further characterized in that it comprises, for a topical administration, a compound derived from titanium and fluorine in a quantity such that the content of titanium is greater than 0.001% by weight, preferably comprised between 0.01 and 0.05% by weight with regard to the total weight of said composition.
7. The composition according to any one of claims 1 to 5, further characterized in that it comprises, for a use designed to reinforce an artificial apatite-based structure, a compound derived from titanium and fluorine in a quantity such that the titanium content is greater than 0.001% by weight, preferably comprised between approximately 0.01 and 0.1% by weight with regard to the total weight of said composition.
8. The composition according to any one of claims 1 to 7, further characterized in that it also comprises an additional fluorinated compound, notably a fluorine salt, for example sodium fluoride or sodium monofluorophosphate, in a quantity varying from approximately 50 ppm to approximately 1500 ppm, preferably from approximately 100 ppm to approximately 500 ppm.
9. The composition according to any one of claims 1 to 8, further characterized in that it is administered by topical route in the form of a dentifrice, a powder to be diluted, a spray, a chewing gum, a lozenge to suck, a gel, an oral implant such as a patch, a mouthwash, or a solution.
10. Use of at least one compound derived from titanium and fluorine conforming to the general formula (I) below:

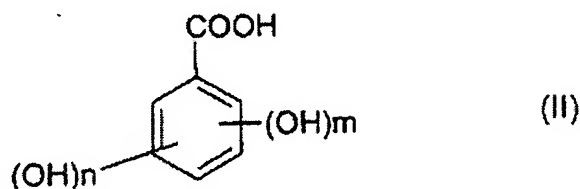


in which

x is a whole number varying from 1 to 6 and y is 0, 1 or 2, with the condition that when y is 0, x is not 4

and R represents:

- a compound chosen from among K, Na or NH_4 , or
- a ligand L of formula (II) below:



in which m is 0 or 1 and n is 0, 1 or 2;

for the reinforcement of apatite-based materials.

11. Use according to claim 10, further characterized in that the composition is such as defined in any one of claims 2 to 9.
12. Use according to claim 10 or 11 for the reinforcement of natural hydroxyapatites, notably dental enamel, dentin, bones, as well as artificial ceramics based on calcium phosphate intended for medical applications, notably dental implants,

devices for percutaneous or periodontal implantation, or bone prostheses used in maxillo-facial or spinal orthopedic surgery.

13. A process for reinforcement of apatite-based materials, comprising the step consisting of applying onto the apatite-based material a composition comprising a titanium and fluorine derivative such as defined in any one of claims 1 to 9, said composition having in the solubilized state a pH less than or equal to 6.
14. The process according to claim 13, further characterized in that, prior to the application of the composition, a step of treatment with an acidic or demineralizing compound is conducted.
15. The process according to claim 14, further characterized in that the acidic or demineralizing compound is notably citric acid, lactic acid, phosphoric acid, or tartaric acid.

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PRELIMINARY SEARCH
REPORT
established on the basis of the last claims
filed before the beginning of the search

National Registration No.
FA 622863
FR 0211062

DOCUMENTS CONSIDERED PERTINENT		Claim(s) concerned	Classification attributed to the invention by INPI
Category	Citation of the document with indication, if necessary, of the pertinent parts		
X, D	WO 01 05797 A (FINIDORI CLAUDINE; SANOFI SYNTHELABO (FR)) January 25, 2001 (01/25/2001) *entire document*	1-9	A 61 K 7/18 C 07 F7/28
A	EP 0 104,640 A (INA SEITO KK) April 4, 1984 (4/4/1984) *page 1, lines 7-15, 20, 32, 35* *page 2, lines 4-6, 16-20* *page 4, lines 24-27* *page 6, lines 34-36* *page 9, lines 2, 3, 8, 9*	1-15	
A	EP 0 116,298 A (OSBORN JOHANNES FRIEDRICH DR) August 22, 1984 (8/22/1984) *claims*	1	
A	WO 00 02830 A (WENGER THOMAS; HECKMANN KLAUSE(DE) NERLICH, MICHAEL (DE)) January 20, 2000 (01/20/2000) *page 3, paragraph 2*	1	
			Technical fields searched (Int. Cl. ⁷)
			A 61 K A 61 L
Date the search was completed June 3, 2003		Examiner Böhm, I	
CATEGORY OF THE DOCUMENTS CITED X: particularly pertinent alone Y: particularly pertinent in combination with another document of the same category A: technological background O: nonwritten disclosure P: guide document		T: theory or principle on which the invention is based E: patent document prior to the filing date that was not published until the filing date or later D: cited in the application L: cited for other reasons &: member of the same family, corresponding document	

ADDENDUM TO THE PRELIMINARY SEARCH REPORT

RELATING TO FRENCH PATENT APPLICATION NO. FR 0211062 FA 622863

The present attachment indicates the members of the patent family relating to the patent documents cited in the preliminary search report indicated above.

Said members are contained in data files of the European Patent Office as of the date of 6/3/2003.

The information provided is given by way of example and is not the responsibility of the European Patent Office or the French administration

Patent document cited in the Search Report		Publication date	Member(s) of the patent family or families	Publication date
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